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Measurement of corneal tangent modulus using ultrasound indentation

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ABSTRACT

Biomechanical properties are potential information for the diagnosis of corneal pathologies. An ultrasound indentation probe consisting of a load cell and a miniature ultrasound transducer as indenter was developed to detect the force–indentation relationship of the cornea. The key idea was to utilize the ultrasound transducer to compress the cornea and to ultrasonically measure the corneal deformation with the eyeball overall displacement compensated. Twelve corneal silicone phantoms were fabricated with different stiffness for the validation of measurement with reference to an extension test. In addition, fifteen fresh porcine eyes were measured by the developed system *in vitro*. The tangent moduli of the corneal phantoms calculated using the ultrasound indentation data agreed well with the results from the tensile test of the corresponding phantom strips ($R^2 = 0.96$). The mean tangent moduli of the porcine corneas measured by the proposed method were 0.089 ± 0.026 MPa at intraocular pressure (IOP) of 15 mmHg and 0.220 ± 0.053 MPa at IOP of 30 mmHg, respectively. The coefficient of variation (CV) and intraclass correlation coefficient (ICC) of tangent modulus were 14.4% and 0.765 at 15 mmHg, and 8.6% and 0.870 at 30 mmHg, respectively. The preliminary study showed that ultrasound indentation could be applied to the measurement of corneal tangent modulus with good repeatability and improved measurement accuracy compared to conventional surface displacement-based measurement method. The ultrasound indentation can be a potential tool for the corneal biomechanical properties measurement *in vivo*.

1. Introduction

Cornea is a transparent tissue which provides about 70% of the eye's optical refraction. The geometric topology of cornea includes shape, thickness and multilayer microstructure that determine refractive effects of the eye. Recently, Laser-Assisted in Situ Keratomileusis (LASIK) has become a popular treatment for correction of refractive errors by changing the thickness of cornea. However, the iatrogenic ectasia has received much attention as the most serious complication in the world after LASIK [1]. Due to the cutting of stroma, keratoconus may potentially be induced immediately or sometime after the surgery among the preoperative keratoconus suspects.

Corneal biomechanical properties were reported to have a close relationship with the pathologies of some corneal degeneration diseases like ectasia [2], keratoconus [3] and pellucid marginal degeneration [4]. The collagen composition and structure of corneal stroma are the controlling factors for corneal biomechanical properties [5,6]. Due to the high tensile stiffness of collagen fibrils and spatially varying distribution of lamellae in the stroma, cornea is a tissue with highly nonlinear, anisotropic, heterogeneous, and viscoelastic characteristics, both laterally and in depth [7]. The biomechanical properties of the cornea are important in maintaining the visual and protection functions of the eye. Evaluations on corneal biomechanical properties include the measurements of corneal rigidity, viscosity, and elasticity. A better understanding of the corneal biomechanical properties is important for corneal pathology diagnosis and prediction of refractive surgery outcome. Many efforts have been devoted to the development of measuring techniques on corneal biomechanical properties, for example, conventional stress–strain measurement [8] and inflation test [9]. However, these methods are not able to be applied to the biomechanical measurement of cornea *in vivo*. Ocular Response Analyzer (ORA, Reichert, Depew, NY, USA) and Corneal Visualization Scheimpflug imaging (CorVis ST, Oculus, Wetzlar, Germany) have been introduced for clinical tests of corneal biomechanical proper-

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ties during the last decade [10,11]. The ORA is a noncontact tonometer which can provide a measure of biomechanical properties of cornea through analyzing corneal response during an air puff. There are useful parameters generated from ORA such as corneal hysteresis (CH) and corneal resistance factor (CRF). CH provides the information about corneal viscoelastic response. CRF may have relationship with elastic properties [12]. The CorVis ST can capture the corneal dynamic deformation under an air puff excitation and gives a direct description of the mechanical behavior of cornea. It was reported that some of the measured parameters such as velocity at applanation, highest concavity, maximum deformation area, corneal contour deformation, and corneal vibration were significantly different when compared between Keratoconic and normal eyes [13,14]. However, ORA cannot provide intrinsic mechanical parameters of cornea [15]. The parameter CH provided by ORA represents the air puff pressure difference between the inward and outward applanations, which is determined not only by the mechanical properties of cornea, but also cornea thickness, geometry, eyeball size, etc. On the other hand, Scheimpflug imaging technique is severely limited by geometrical and optical distortions which make careful corrections necessary beyond the quantitative extraction of biomechanics related information [16]. Recently it has been theoretically verified that a comprehensive correction would be required to obtain an accurate deformation measurement of the cornea using this technique [17].

Corneal biomechanical properties are also closely correlated with the intraocular pressure (IOP) measurement, which is an essential indicator for the diagnosis and management strategy of glaucoma, one of the leading causes of irreversible blindness. The traditional measurement methods on IOP are based on the classical Imbert-Fick principle, such as Goldman applanation tonometry (GAT) [18], TonoPen [19], and dynamic contour tonometry (DCT) [20]. But none of them can provide the corneal elasticity measurement. Ultrasonic methods were reported previously for the measurement of corneal biomechanical properties. Corneal speed of sound can be measured to analyze the corneal properties [21]. Aggregate modulus can be calculated based on the speed of ultrasound to determine the change of corneal mechanical properties [22]. In addition, corneal elastic property could be evaluated by an ultrasonic system based on a modeling of the wave propagation at the two corneal interfaces [23]. Porcine corneal stiffness measured using this technique was reported to have a significant increase after collagen crosslinking treatment [24]. Shear wave was generated by using ultrasound system to detect the Young's modulus of corneal sample as reported in the literature [25] and later shear wave induced by acoustic radiation force was utilized to measure the corneal mechanical properties [26]. However, due to various reasons, these techniques have not become clinically mature yet; for example, acoustic radiation force based shear wave propagation method may have concern of safety issue. Efforts are still needed to develop appropriate tools for safe, convenient and accurate measurement of corneal mechanical properties. It has been recently reported that corneal mechanical indentation combining a load sensor and a linear actuator could be used to measure corneal tangent modulus on porcine and rabbit corneas [27]. Using the mechanical indentation, the displacement of cornea surface (calculated from the movement of the head of the indenter driven by the linear actuator) was treated as the corneal deformation; however, the result may not be accurate as any movement of the whole eyeball under the applied force would be counted into the corneal deformation. Therefore, additional development is required to solve this inherent problem of the mechanical indentation method.

Ultrasound indentation is a potential technique which can solve the bulk movement issue for accurate deformation measurement during the corneal indentation test. In ultrasound indentation the probe normally consists of a load cell connected in series with an ultrasound transducer as the indenter [28]. The tissue thickness and indentation deformation can be measured by ultrasound signal reflected from internal tissue interface. This method has been widely used for the stiffness measurement of soft tissues *in vivo* such as residual limb [29], diabetic foot [30], post-radiotherapy fibrotic neck [31] and lower back [32]. However, few studies have been reported in the literature on the use of ultrasound indentation for corneal biomechanical measurement. Normally, the size of conventional ultrasound transducer is too big to be applied on cornea with curvature, in consideration of both complicated contact condition and high risk in causing damage to the cornea for a big ultrasound transducer. This problem can be solved by adopting a small profile ultrasound transducer. In addition, as the ultrasound indentation uses the internal tissue interface as the reference for the extraction of deformation during indentation, the measurement result will not be affected by the bulk movement of the tested tissue such as the eyeball in corneal testing, which improves the measurement accuracy. Therefore, ultrasound indentation has the potential for measuring the corneal biomechanical properties with improved accuracy compared to traditional indentation. In this paper, we developed an ultrasound indentation method using a portable ultrasound indentation system with a miniature ultrasound transducer to measure corneal tangent modulus. For method validation, a series of tissue mimicking phantoms with different stiffness were fabricated and tested with ultrasound indentation, and the results were compared to those by a reference extension test. Preliminary tests were also conducted on 15 porcine corneal eyeballs *in vitro* in order to demonstrate the feasibility of the proposed testing method on corneal biomechanical test.

2. Materials and methods

2.1. Ultrasound indentation system

The developed ultrasound indentation probe was similar to that in our previous reports [28–30] except that a small profile ultrasound transducer was adopted for appropriate operation on cornea. An ultrasound transducer with a frequency of 10 MHz and a diameter of 3 mm (Model: V129-SM, Panametrics, Olympus, MA, USA) was used to build a hand-held pen-sized indentation probe. A compressive load cell (Model: ELFS-T3E-2L, Entran Devices Inc., Fairfield, NJ, USA) was connected in series with the ultrasound transducer as a force sensor to record the indentation force. The information of cornea such as the anterior chamber depth and corneal displacement was extracted by the ultrasound signals during indentation. A custom-designed program developed by Microsoft VC++ was responsible for data collection and analysis in which the force and ultrasound signal were used to calculate corneal biomechanical properties. All the data were recorded during corneal experiment and further analyzed offline to obtain the biomechanical parameters.

2.2. Phantoms and porcine eyes preparation

Silicone phantoms were fabricated to mimic the structure of cornea. The phantoms were designed with a central thickness of 500 μm and a peripheral thickness of 1000 μm, respectively. The curvature radius of the anterior surface was 8 mm and that of the aspherical posterior surface changed from 6 mm to 7 mm, consequently, in the direction from center to periphery. The diameter of corneal part was designed to be 12 mm and the depth of the unloaded anterior segment was 3.8 mm (Fig. 1). To mimic different corneal elasticity under different physiological and pathological status or among different subjects, corneal phantoms with differ-